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TRANSLATION:

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(54) Title of the Invention:

SUBSTANCE CONSISTING OF HOST/GUEST COMPLEXES WHICH FORM CAVITANDS OR CLATHRATES, USED AS A CONTRAST MEDIUM

(57) Abstract

The invention concerns the use of host/guest complexes which form cavitands or clathrates as a contrast medium in ultrasonic, radiological, or NMR investigations.

Substance consisting of host/guest complexes which form cavitands or clathrates, used as a contrast medium.

The invention concerns a substance consisting of host/guest complexes which form cavitands or clathrates, as described in Claim 1.

The production of stoichiometric host/guest complexes, consisting of host molecules, essentially organic onium compounds, and gases or gas-producing substances as guest molecules, is described in the literature [*Angew. Chem.*, Vol. 97, p. 721, 1985]. Use of the host/guest complexes as a contrast medium is not described.

The object of the invention is to provide a substance that can be used as a transport medium for contrast media for ultrasonic, radiological, or NMR investigations. In particular, the objective of the invention is to provide host/guest complexes that store the greatest possible volume of guest in a minimum weight of host.

Surprisingly, it was found that the cavitands or clathrates cited in Claim 1 constitute a transport medium that dissolves completely and can be selected in such a way that it has no toxic effects at all on the biological material in which the investigation is to be conducted.

Preferably, the substance used for ultrasonic investigations can contain, as the host molecules:

Water, urea and its derivatives, thiourea and its derivatives, phenol and substituted phenols, dihydroxybenzenes and their derivatives, hydroquinone and substituted hydroquinones, salicylic acid and its derivatives, tri-o-thymotide and its derivatives, ascorbic acid, flavins and their derivatives, flavanols and their derivatives, cyclophanes and their derivatives, guayacanin, naphthohydroquinones and their derivatives, cyclodextrin and its derivatives, especially dimethyl-1-cyclodextrin, methyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, chromans and their derivatives, especially 4-*p*-hydroxyphenyl-2,2,4-trimethylchroman, 4-*p*-hydroxyphenyl-2,2,4-trimethylthiochroman, 4-*p*-hydroxyphenyl-2,2,4,7-tetramethylthiochroman, 4-*p*-hydroxy phenyl-2,2,4-trimethylselenium chroman, hexahost compounds, especially hexakis-(phenylthio)benzene and its derivatives, cyclotriveratrylene and its derivatives, 1,1'-binaphthyl-2,2'-dicarboxylic acid and its derivatives, onium compounds and their derivatives, acetylsalicylic acid, di-, tri-, and tetrasalicylides, 9,9'-spirobifluorene-2,2'-dicarboxylic acid, choleic acids, 4,4'-dinitrodiphenyl, bis(*N*,*N*'-alkylene benzidine), bis(*N*,*N*'-tetramethylene benzidine), desoxycholic acid, monoaminonickel(III) cyanide, tetra(4-methylpyridine) nickel(II) dithiocyanates and their derivatives, hexamethylisocyanidoferrochlorides, 2-phenyl-3-*p*-(2,2,4-trimethylchroman-4-yl)phenyl-4-quinazoline, cyclotriphosphazones, tris-1,2,phenyldioxy-cyclotriphosphazones and as guest molecules:

Noble gases and noble gas compounds, sulfur halides, nitrogen and nitrogen oxides, carbon oxides, hydrogen and hydrogen oxides, sulfur oxides, phosphorus hydrides, hydrogen halides, uranium halides, and oxygen, as well as hydrocarbons and their derivatives, epoxides, ethers, and halogenated hydrocarbons.

Particularly preferably, the substance used for ultrasonic investigation can contain as guest molecules helium, neon, argon, krypton, xenon, radon, sulfur hexafluoride, water, hydrogen peroxide, nitrogen monoxide, carbon monoxide, carbon dioxide, hydrogen iodide, xenon difluoride, xenon tetrafluoride, xenon hexafluoride, xenon dioxide, sulfur dioxide, sulfur trioxide, arsenic trihydride, phosphorus hydride, deuterium, uranium hexafluoride, methane, ethane, propane, cyclopropane, butane, pentane, ethylene oxide, and methyl bromide.

The particle size of the crystalline complexes can be influenced, particularly by the crystallization conditions, and also by mechanical methods of particle size reduction (air jet grinding).

The crystalline complexes can be coated with hydrophilic, lipophilic, or amphiphilic auxiliary agents.

Suitable as vehicles for applying the complexes are sterile aqueous systems with additives to adjust the viscosity, surface tension, pH value, and osmotic pressure, in which the complexes preferably are dissolved before use, but can also be suspended and possibly emulsified.

The host/guest complexes are introduced into an aqueous vehicle. Because the host molecules dissolve, the complexes are destroyed and the gas bubbles are released into the vehicle. The host molecules dissolved in the vehicle no longer have any complexing properties. The rate of gas release and the size and duration of the gas bubbles can be controlled within a wide range by adjusting the nature of the enclosed gas or gas-producing substance, the nature of the host molecule, and the surface area or particle size as a function of the viscosity and surface tension of the vehicle.

Thus, surprisingly, it is possible to obtain injectable gas-containing pharmaceutical preparations with pronounced echogenic properties by a very simple method.

In particular, it is possible to prepare the amount of gas required for *in vivo* contrasting of, for example, the left ventricle in humans, namely ca. 150 μL, with very small amounts of the active substance, in the range of 2-10 mg/application, as shown in the following summary:

TABLE 1. KEY: (a) hydroquinone/N_2; (b) complex; (c) hydroquinone/Xe; (d) Dianin's compound/SF_6; (e) Dianin's compound/argon; (f) tri-*o*-thymotide/methane; (g) tri-*o*-thymotide CH_3Br; and (h) Dianin's compound/N_2.

(a)	Hydrochinon/N_2	3:1 Komplex	1 mg	70 µl
(c)	Hydrochinon/Xe	3:1 " (b)	1 mg	53 µl
(d)	Dianin/SF_6	3:1 "	1 mg	28 µl
(e)	Dianin/Argon	2:1 "	1 mg	28 µl
(f)	Tri-o-Thymotide/Methan	2:1 "	1 mg	23 µl
(g)	Tri-o-Thymotide CH_3Br	2:1 "	1 mg	21 µl
(h)	Dianin/N2		1 mg	103 µl

4-(4-hydroxyphenyl)-2,2,4-trimethylchroman is called Dianin's compound, and is prepared as described in the literature [*J. Russ Phys. Chem. Soc.*, Vol. 46, p. 1,310, 1914 and *Chem. Zentr.* Vol. I, p. 1,063, 1915].

Thus it is possible to provide a contrast medium for ultrasonic diagnosis which, after intravenous injection, allows ultrasonic visualization of the blood and its flow conditions on the right side of the heart and, after its passage through the pulmonary capillary bed, on the left side of the heart. Furthermore, it should also allow visualization of the flow of blood to other organs, such as the myocardium, liver, spleen, and kidneys. Likewise, it can

be used for visualization of the efferent urinary tract and the gastrointestinal tract, the joints, the frontal sinus, and the eyes.

Especially when gas molecules (for example xenon) that are capable of crossing the blood/brain barrier are used, ultrasonic visualization of the brain and its physiological and pathological structures is possible.

If the substance according to the invention contains xenon, for example, this host/guest complex can be used as a radiological contrast medium. If stable radicals (for example, oxygen or nitroxyl radicals) are used, the substances according to the invention can also be used as NMR contrast media.

The invention is described in greater detail with the following examples:

1. TRI-*o*-THYMOTIDE/METHYL BROMIDE

Tri-*o*-thymotide (25 g) was dissolved in 2,2,4-trimethylpentane (50 mL) at 100°C and the hot solution was placed in a high-pressure autoclave. Methyl bromide was introduced into the autoclave until a pressure of 200 bars was reached. The high-pressure autoclave was kept at 110°C for 2 hours and then the solution was cooled at room temperature for 5 days. The crystals were filtered off and washed three times with cold 2,2,4-trimethylpentane; then the crystals were dried in a drying oven at 50°C.

2. DIANIN'S COMPOUND (4-*p*-HYDROXYPHENYL-2,2,4-TRIMETHYLCHROMAN)/ ETHYLENE OXIDE

Dianin's compound (25 g) was dissolved in 1-decanol (35 g) at 125°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed ethylene oxide to 300 bars. The high-pressure auto-

clave was kept at 140°C for 2 hours, then the solution was cooled at room temperature for 8 days. The crystals were filtered off and washed four times with cold 1-decanol (5 mL); then the crystals were dried in a drying oven at 100°C.

3. DIANIN'S COMPOUND (4-*p*-HYDROXYPHENYL-2,2,4-TRIMETHYLCHROMAN)/ SULFUR HEXA FLUORIDE

Dianin's compound (25 g) was dissolved in 1-decanol (35 g) at 125°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed ethylene oxide to 300 bars. The high-pressure autoclave was kept at 140°C for 2 hours, then the solution was cooled at room temperature for 8 days. The crystals were filtered off and washed four times with cold 1-decanol (5 mL); then the crystals were dried in a drying oven at 100°C.

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Dianin's compound (25 g) was dissolved in 1-decanol (35 g) at 125°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed xenon to 300 bars. The high-pressure autoclave was kept at 140°C for 2 hours, then the solution was cooled at room temperature over 8 days. The crystals were filtered off and washed four times with cold 1-decanol (5 mL); then the crystals were dried in a drying oven at 100°C.

11. DIANIN'S COMPOUND (4-*p*-HYDROXYPHENYL-2,2,4-TRIMETHYLCHROMAN)/ARGON

Dianin's compound (25 g) was dissolved in 1-decanol (35 g) at 125°C. The hot solution was placed in a high-pressure autoclave. The solution was pres-

surized with compressed argon to 300 bars. The high-pressure autoclave was kept at 140°C for 2 hours, then the solution was cooled at room temperature for 8 days. The crystals were filtered off and washed four times with cold 1-decanol (5 mL); then the crystals were dried in a drying oven at 100°C. Melting point: 160.84°C.

12. HYDROQUINONE/METHANE

Hydroquinone (30 g) was dissolved in *n*-propanol (70 mL) at 70°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed methane to 300 bars. The high-pressure autoclave was kept at 80°C for 2 hours, then the solution was cooled at room temperature for 5 days. The crystals were filtered off and washed four times with cold *n*-propanol (5 mL); then the crystals were dried in a drying oven at 70°C.

13. HYDROQUINONE/SULFUR HEXAFLUORIDE

Hydroquinone (30 g) was dissolved in *n*-propanol (70 mL) at 70°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed sulfur hexafluoride to 300 bars. The high-pressure autoclave was kept at 80°C for 2 hours, then the solution was cooled at room temperature for 5 days. The crystals were filtered off and washed four times with cold *n*-propanol (5 mL); then the crystals were dried in a drying oven at 70°C.

14. HYDROQUINONE/PROPANE

Hydroquinone (30 g) was dissolved in *n*-propanol (70 mL) at 70°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed propane to 300 bars. The high-pressure autoclave was kept at 80°C for 2 hours, then the solution was cooled at room temperature for 5 days. The crystals were filtered off and washed four times with cold *n*-propanol (5 mL); then the crystals were dried in a drying oven at 70°C.

15. HYDROQUINONE/ETHANE

Hydroquinone (30 g) was dissolved in *n*-propanol (70 mL) at 70°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed ethane to 300 bars. The high-pressure autoclave was kept at 80°C for 2 hours, then the solution was cooled at room temperature for 5 days. The crystals were filtered off and washed four times with cold *n*-propanol (5 mL); then the crystals were dried in a drying oven at 70°C.

16. HYDROQUINONE/CARBON DIOXIDE

Hydroquinone (30 g) was dissolved in *n*-propanol (70 mL) at 70°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed carbon dioxide to 300 bars. The high-pressure autoclave was kept at 80°C for 2 hours, then the solution was cooled at room temperature for 5 days. The crystals were filtered off and washed four times with cold *n*-propanol (5 mL); then the crystals were dried in a drying oven at 70°C.

17. HYDROQUINONE/ETHYLENE OXIDE

Hydroquinone (30 g) was dissolved in *n*-propanol (70 mL) at 70°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed ethylene oxide to 300 bars. The high-pressure autoclave was kept at 80°C for 2 hours, then the solution was cooled at room temperature for 5 days. The crystals were filtered off and washed four times with cold *n*-propanol (5 mL); then the crystals were dried in a drying oven at 70°C.

18. HYDROQUINONE/CYCLOPROPANE

Hydroquinone (30 g) was dissolved in *n*-propanol (70 mL) at 70°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed cyclopropane to 300 bars. The high-pressure autoclave was kept at 80°C for 2 hours, then the solution was cooled at room temperature for 5 days. The crystals were filtered off and washed four times with cold *n*-propanol (5 mL); then the crystals were dried in a drying oven at 70°C.

19. HYDROQUINONE/NITROGEN

Hydroquinone (30 g) was dissolved in *n*-propanol (70 mL) at 70°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed nitrogen to 300 bars. The high-pressure autoclave was kept at 80°C for 2 hours, then the solution was cooled at room temperature for 5 days. The crystals were filtered off and washed four times with cold *n*-propanol (5 mL); then the crystals were dried in a drying oven at 70°C. Melting point: 178.92°C.

20. HYDROQUINONE/XENON

Hydroquinone (30 g) was dissolved in *n*-propanol (70 mL) at 70°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed xenon to 300 bars. The high-pressure autoclave was kept at 80°C for 2 hours, then the solution was cooled at room temperature for 5 days. The crystals were filtered off and washed four times with cold *n*-propanol (5 mL); then the crystals were dried in a drying oven at 70°C.

21. HYDROQUINONE/ARGON

Hydroquinone (30 g) was dissolved in *n*-propanol (70 mL) at 70°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed argon to 300 bars. The high-pressure autoclave was kept at 80°C for 2 hours, then the solution was cooled at room temperature for 5 days. The crystals were filtered off and washed four times with cold *n*-propanol (5 mL); then the crystals were dried in a drying oven at 70°C. Melting point: 175.67°C.

22. UREA/BUTANE

4 g urea was dissolved in 12 mL of ethanol at 60°C, then the solution was placed in a high-pressure autoclave and pressurized with butane to 150 bars. The solution was cooled from 80°C to room temperature over 48 hours. The solution with H/G crystals was removed from the autoclave, filtered, and the H/G crystals were washed with 10 mL of cold ethanol. The H/G complex crystals were dried in a vacuum oven at 60°C.

23. UREA/ISOBUTANE

4 g urea was dissolved in 12 mL of ethanol at 60°C, then the solution was placed in a high-pressure autoclave and pressurized with isobutane to 150 bars. The solution was cooled from 80°C to room temperature over 48 hours. The solution with H/G crystals was removed from the autoclave, filtered, and the H/G crystals were washed with 10 mL of cold ethanol. The H/G complex crystals were dried in a vacuum oven at 60°C. Melting point: 138.50°C.

24. UREA/NEOPENTANE

4 g urea was dissolved in 12 mL of ethanol at 60°C, then the solution was placed in a high-pressure autoclave and pressurized with neopentane to 150 bars. The solution was cooled from 80°C to room temperature over 48 hours. The solution with H/G crystals was removed from the autoclave, filtered, and the H/G crystals were washed with 10 mL of cold ethanol. The H/G complex crystals were dried in a vacuum oven at 60°C. Melting point: 138.79°C.

25. THIOUREA/BUTANE

4 g thiourea was dissolved in 12 mL of ethanol at 60°C, then the solution was placed in a high-pressure autoclave and pressurized with butane to 150 bars. The solution was cooled to room temperature over 60 hours. The solution with H/G crystals was removed from the autoclave, filtered, and the H/G crystals were washed with 10 mL of cold ethanol. The H/G complex crystals were dried in a vacuum oven at 60°C.

26. THIOUREA/ISOBUTANE

4 g thiourea was dissolved in 20 mL of ethanol at 60°C, then the solution was placed in a high-pressure autoclave and pressurized with isobutane to 150 bars. The solution was cooled to room temperature over 60 hours. The solution with H/G crystals was removed from the autoclave, filtered, and the H/G crystals were washed with 10 mL of cold ethanol. The H/G complex crystals were dried in a vacuum oven at 60°C. Melting point: 181.34°C.

27. THIOUREA/NEOPENTANE

4 g thiourea was dissolved in 20 mL of ethanol at 60°C, then the solution was placed in a high-pressure autoclave and pressurized with neopentane to 150 bars. The solution was cooled to room temperature over 60 hours. The solution with H/G crystals was removed from the autoclave, filtered, and the H/G crystals were washed with 10 mL of cold ethanol. The H/G complex crystals were dried in a vacuum oven at 60°C.

28. VEHICLE

A: Examples of suitable vehicles for hydroquinone, tri-*o*-thymotide-urea, and thiourea H/G complexes are the following solutions:

(a) 1% gelatin solution;

(b) 1% albumin solution;

(c) 10% glycerin solution;

(d) 15% propylene glycol solution;

(e) mixtures of sodium cholate and phosphatidylcholine in water;

(f) 0.01-1% phosphatidylcholine dispersion (aqueous);

(g) 1% methylcellulose;

(h) 1-2% dextran solution;

(i) 1% agar solution;

(j) 2% Tween solution (Tween 80);

(k) 1% gum arabic.

B: Examples of suitable vehicles for Dianin's compound H/G complexes are the following:

(a) 10-20% 2-(2-methoxyethoxy)ethanol;

(b) mixtures of 2-(2-methoxyethoxy)ethanol (20%) and Tween 80 (1%).

IN VITRO ULTRASONIC INVESTIGATIONS

The acoustic properties of the H/G-complex-vehicle systems were determined with *in vitro* ultrasonic investigations.

For this purpose, ca. 1-5 mg of the H/G complexes in 10-20 mL was mixed with one of the vehicles listed and then investigated with ultrasonic scanners.

For qualitative investigations, the Ekoline 20A/S ultrasonic scanner was used in the frequency range 1-5 MHz.

Quantitative measurements of the acoustic properties were obtained in an apparatus with the Kraut-Kraemer U.S.I. P-12 ultrasonic scanner at 4 MHz. The results for four systems are presented here as examples (Figures 1-4).

Figure 1: Urea/isobutane (Example 23) in 2% Tween 80 solution;

Figure 2: Thiourea/isobutane (Example 26) in 1% dextran solution;

Figure 3: Hydroquinone/argon (Example 21) in 1% gelatin solution;

Figure 4: Dianin's compound/argon (Example 21) in 10% 2-(2-methoxy-

ethoxy)ethanol.

Explanation of the ultrasonic measurement apparatus and the figures obtained from it:

The apparatus consists of an ultrasonic transmitter combined with a receiver and a measurement cell containing the sample. To measure the acoustic properties of the sample, an ultrasonic impulse is transmitted. Backscattered ultrasound is measured by the receiver and indicated by a change in amplitude (see figures). Each of the figures shows only one change in amplitude, caused by backscattering of the ultrasound on the front wall of the measurement cell. A second change in amplitude, caused by backscattering on the rear wall of the measurement cell, is obtained only with non-echogenic substances (for example, water). In the case of echogenic substances, no second backscattering signal is obtained, because the ultrasound dissipates in the sample, or is so altered that it can no longer be received.

CLAIM(S)

1. Substance consisting of host/guest (H/G) complexes which form cavitand s or clathrates, whose host molecules dissolve in a liquid vehicle, releasing the guest, as a contrast medium in ultrasonic, radiological, or NMR investigations.

2. Substance as described in Claim 1 used for ultrasonic investigations, containing as the host molecules:

Water, urea and its derivatives, thiourea and its derivatives, phenol and substituted phenols, dihydroxybenzenes and their derivatives, hydroquinone and substituted hydroquinones, salicylic acid and its derivatives, tri-*o*-thymotide and its derivatives, ascorbic acid, flavins and their derivatives, flavanols

and their derivatives, cyclophanes and their derivatives, guayacanin, naphthohydroquinones and their derivatives, chromans and their derivatives, especially 4-*p*-hydroxyphenyl-2,2,4-trimethylchroman, 4-*p*-hydroxyphenyl-2,2,4- trimethylthiochroman, 4-*p*-hydroxyphenyl-2,2,4,7-tetramethylthiochroman, 4-*p*-hydroxyphenyl-2,2,4-trimethylselenium chroman, hexahost compounds, especially hexakis(phenylthio)benzene and its derivatives, cyclotriveratrylene and its derivatives, 1,1'-binaphthyl-2,2'-dicarboxylic acid and its derivatives, onium compounds and their derivatives, acetylsalicylic acid, di-, tri-, and tetrasalicylides, 9,9'-spirobifluorene-2,2'-dicarboxylic acid, choleic acids, 4,4'-dinitrodiphenyl, bis-(*N*,*N*'-alkylene benzidine), bis-(*N*,*N*'-tetramethylene benzidine), desoxycholic acid, monoaminonickel(III) cyanide, tetra(4-methylpyridine) nickel(II) dithiocyanates and their derivatives, hexamethylisocyanidoferrochlorides, 2-phenyl-3-*p*-(2,2,4-trimethyl-chroman-4-yl)phenyl-4-quinazoline, cyclotriphosphazones, tris-1,2,phenyldioxycyclotriphosphazones, and as guest molecules:

Noble gases and noble gas compounds, sulfur halides, nitrogen and nitrogen oxides, carbon oxides, hydrogen and hydrogen oxides, sulfur oxides, phosphorus hydrides, hydrogen halides, uranium halides, and oxygen, as well as hydrocarbons and their derivatives, epoxides, ethers, and halogenated hydrocarbons.

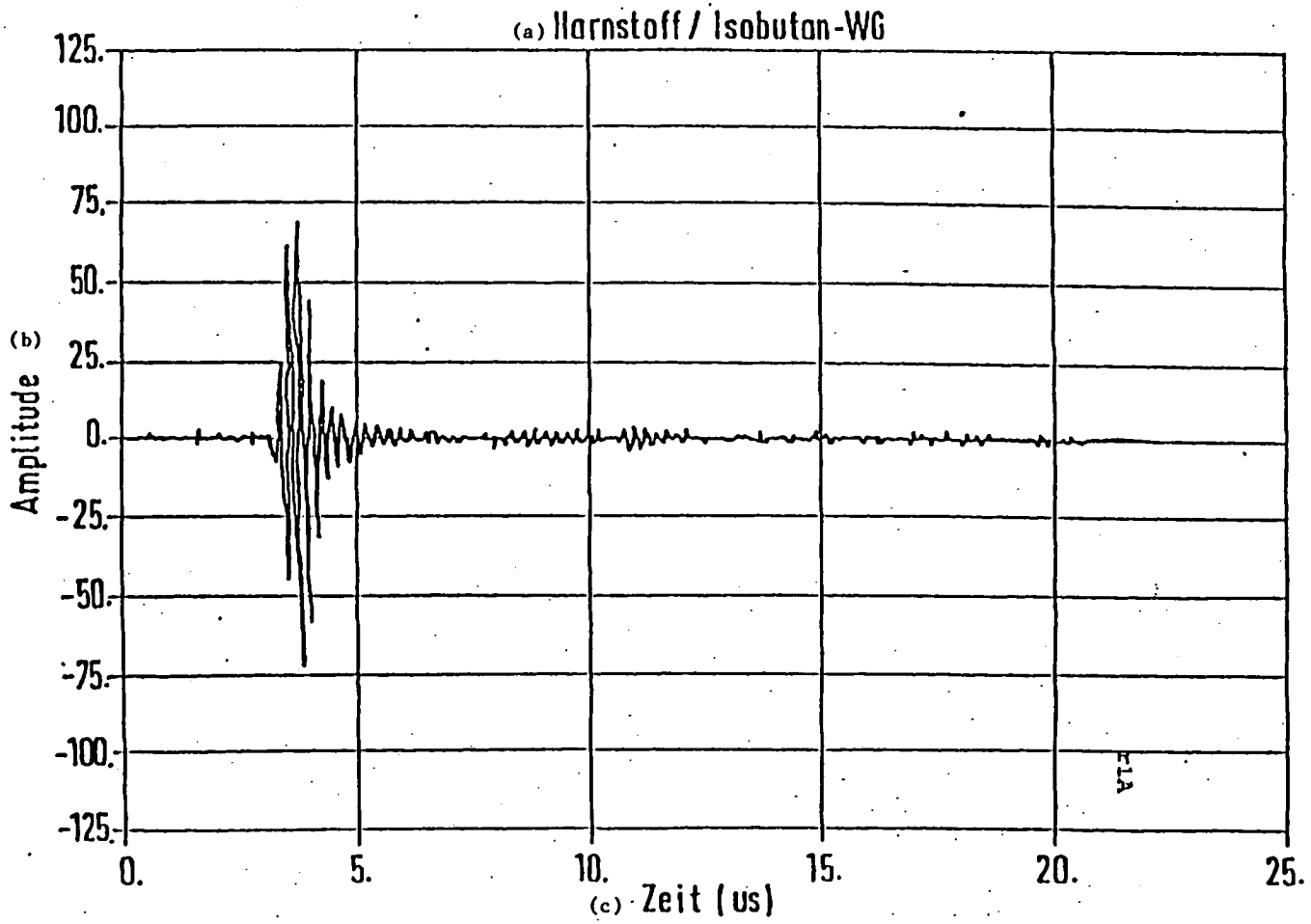

Figure 1. KEY: (a) urea/isobutane H/G; (b) amplitude; and (c) time (microseconds).

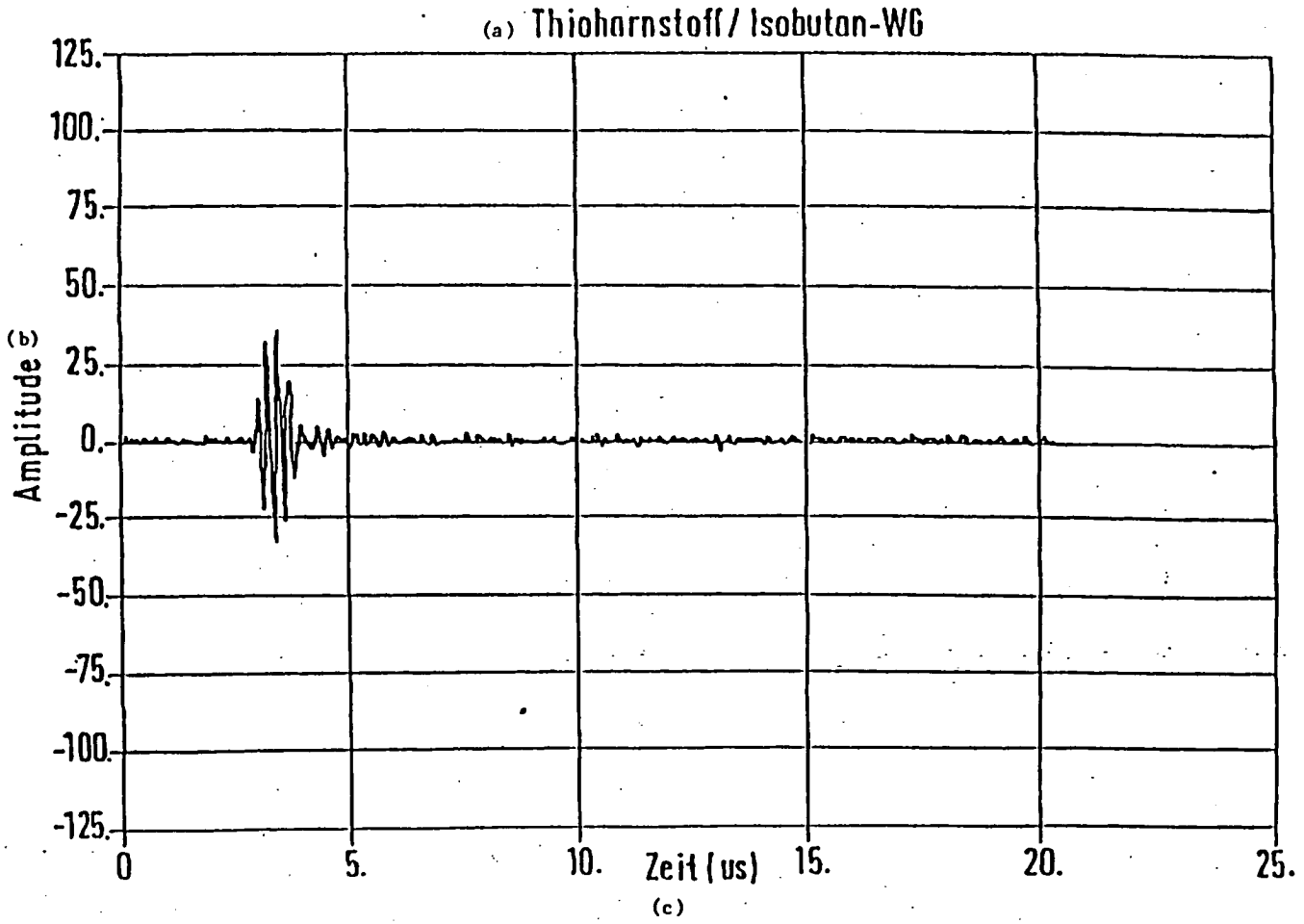

Figure 2. KEY: (a) thiourea/isobutane H/G; (b) amplitude; and (c) time (μs).

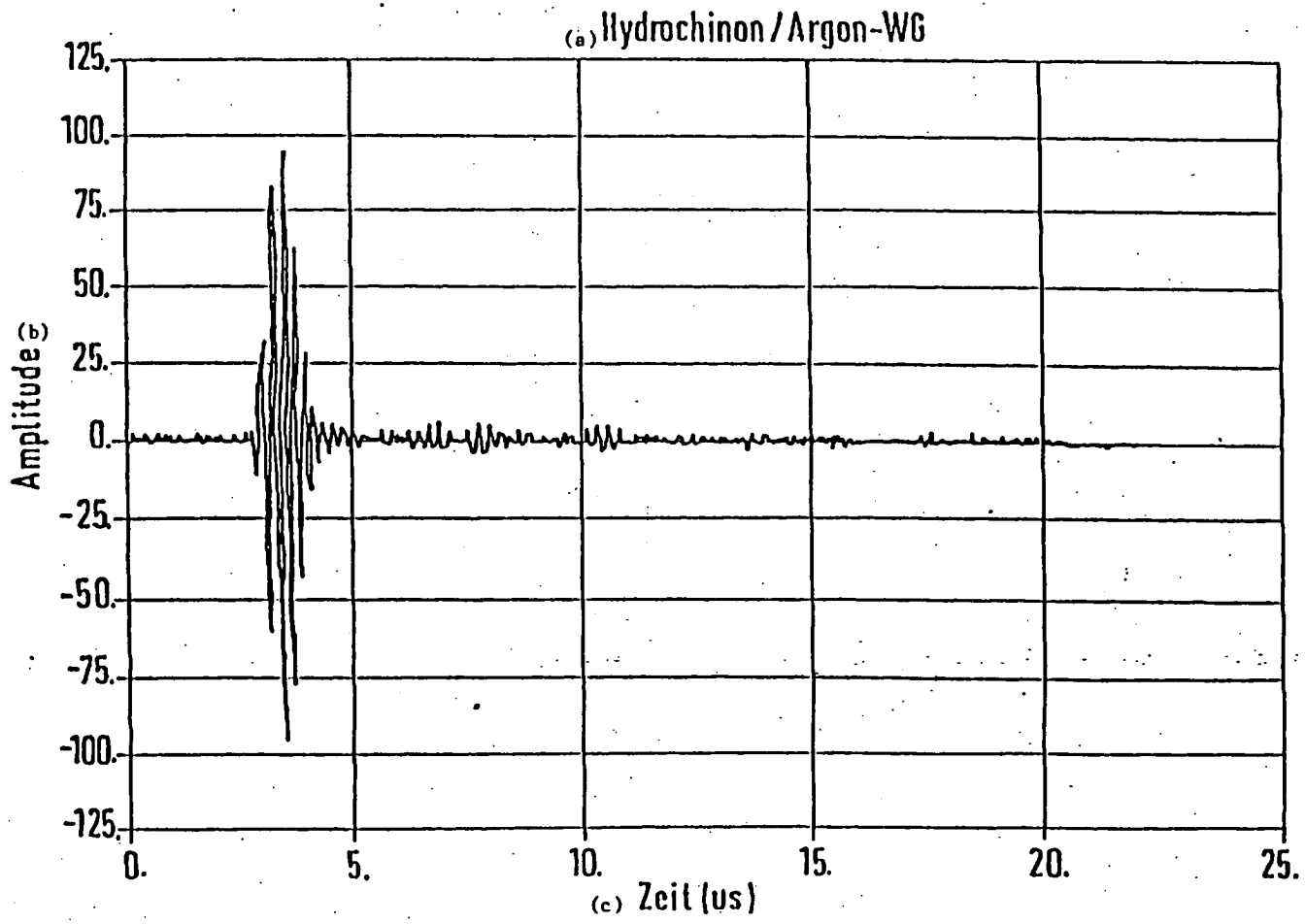

Figure 3. KEY: (a) hydroquinone/argon H/G; (b) amplitude; and (c) time (microseconds).

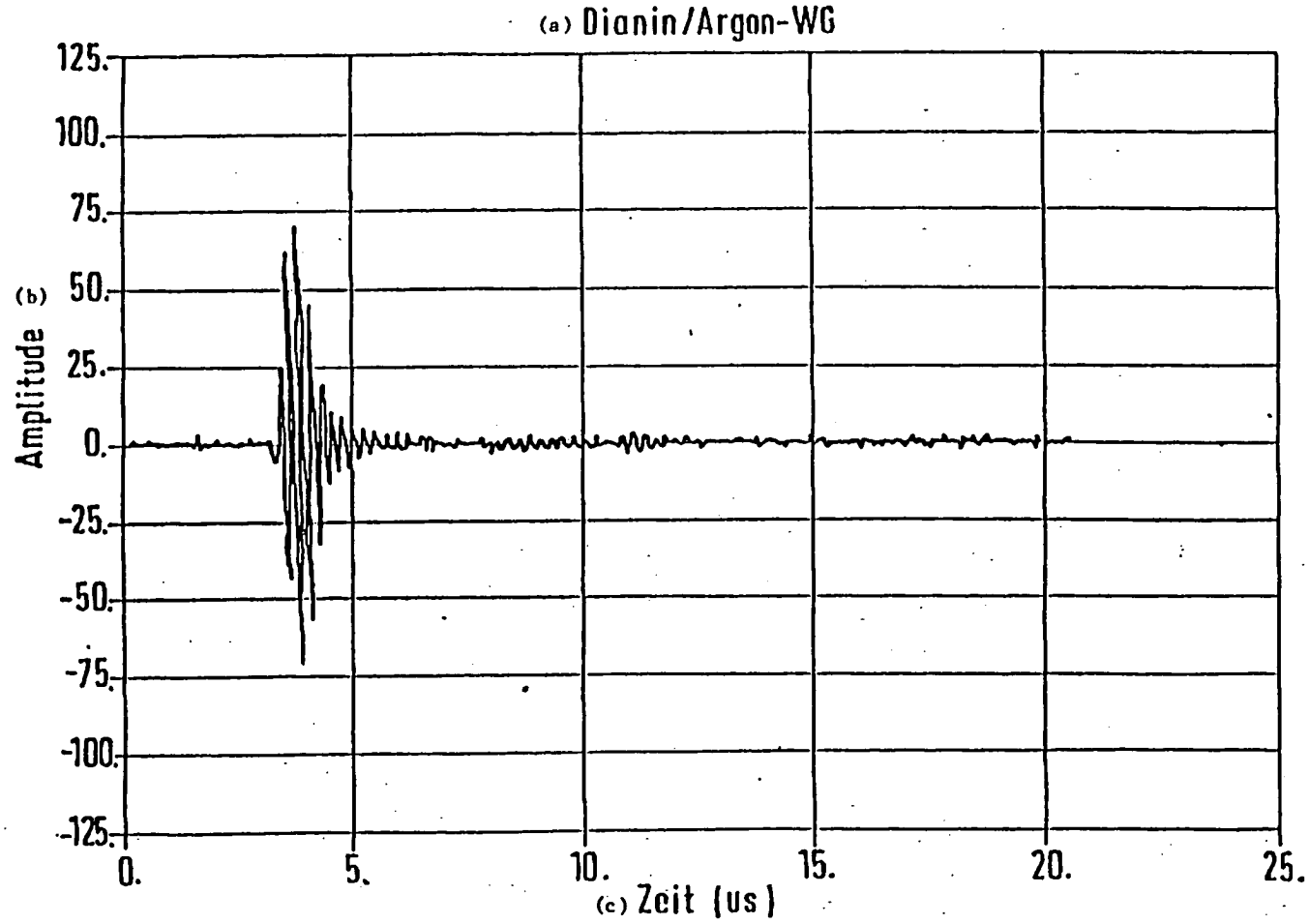

Figure 4. KEY: (a) Dianin's compound/argon H/G; (b) amplitude; and (c) time (microseconds).

European Patent Office

Application No.

EUROPEAN SEARCH REPORT

RELEVANT DOCUMENTS

Category	Citation of document with indication, where appropriate, of the relevant passages	Relevant to Claim No.	Classification of the application (Int. Cl.[5])
A	Patent Abstracts of Japan, Vol. 5, No. 160, (C-75)[832] October 15, 1981; & JP-A-56 92 221 (ZERIA SHINYAKU KOGYO K.K.) July 15, 1981.		A 61 K 49/00 A 61 K 49/04
A	WO-A-8 002 356 (RASOR ASSOCIATES INC.)		
A	EP-A-0 224 934 (S.B. FEINSTEIN)		
A	DE-A-3 637 926 (SCHERING AG)		

Fields searched (Int. Cl.[5])

A 61 K

The present search report has been prepared for all of the patent claims.

Location of search:	Date of completion of search:	Examiner:
The Hague	November 21, 1989	C. Alvarez y Alvarez

CATEGORY OF CITED DOCUMENTS

X: of particular relevance considered alone

Y: of particular relevance in connection with another publication of the same category

A: technological background

O: unwritten disclosure

P: interim document

T: theories or principles on which the invention is based

E: earlier document, but published on or after the filing date

D: document cited in the application

L: document cited for other reasons

&: member of the same patent family, corresponding document

PARTIAL TRANSLATION:

(19) European Patent Office (11) Document No.: 357,163 A1

Foreign page 5 which was missing from the translation follows:

4. DIANIN'S COMPOUND (4-*p*-HYDROXYPHENYL-2,2,4-TRIMETHYLCHROMAN)/ ETHANE

Dianin's compound (25 g) was dissolved in 1-decanol (35 g) at 125°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed ethane to 300 bars. The high-pressure autoclave was kept at 140°C for 2 hours, then the solution was cooled at room temperature for 8 days. The crystals were filtered off and washed four times with cold 1-decanol (5 mL); then the crystals were dried in a drying oven at 100°C.

5. DIANIN'S COMPOUND (4-*p*-HYDROXYPHENYL-2,2,4-TRIMETHYLCHROMAN)/ PROPANE

Dianin's compound (25 g) was dissolved in 1-decanol (35 g) at 125°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed propane to 300 bars. The high-pressure autoclave was kept at 140°C for 2 hours, then the solution was cooled at room temperature for 8 days. The crystals were filtered off and washed four times with cold 1-decanol (5 mL); then the crystals were dried in a drying oven at 100°C.

6. DIANIN'S COMPOUND (4-*p*-HYDROXYPHENYL-2,2,4-TRIMETHYLCHROMAN)/ CARBON DIOXIDE

Dianin's compound (25 g) was dissolved in 1-decanol (35 g) at 125°C. The

hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed carbon dioxide to 300 bars. The high-pressure autoclave was kept at 140°C for 2 hours, then the solution was cooled at room temperature for 8 days. The crystals were filtered off and washed four times with cold 1-decanol (5 mL); then the crystals were dried in a drying oven at 100°C.

7. DIANIN'S COMPOUND (4-*p*-HYDROXYPHENYL-2,2,4-TRIMETHYLCHROMAN)/ CYCLOPROPANE

Dianin's compound (25 g) was dissolved in 1-decanol (35 g) at 125°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed cyclopropane to 300 bars. The high-pressure autoclave was kept at 140°C for 2 hours, then the solution was cooled at room temperature for 8 days. The crystals were filtered off and washed four times with cold 1-decanol (5 mL); then the crystals were dried in a drying oven at 100°C.

8. DIANIN'S COMPOUND (4-*p*-HYDROXYPHENYL-2,2,4-TRIMETHYLCHROMAN)/ METHANE

Dianin's compound (25 g) was dissolved in 1-decanol (35 g) at 125°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed methane to 300 bars. The high-pressure autoclave was kept at 140°C for 2 hours, then the solution was cooled at room temperature for 8 days. The crystals were filtered off and washed four times with cold 1-decanol (5 mL); then the crystals were dried in a drying oven at 100°C.

9. DIANIN'S COMPOUND (4-*p*-HYDROXYPHENYL-2,2,4-TRIMETHYLCHROMAN)/ NITROGEN

Dianin's compound (25 g) was dissolved in 1-decanol (35 g) at 125°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed nitrogen to 300 bars. The high-pressure autoclave was kept at 140°C for 2 hours, then the solution was cooled at room temperature for 8 days. The crystals were filtered off and washed four times with cold 1-decanol (5 mL); then the crystals were dried in a drying oven at 100°C.

10. DIANIN'S COMPOUND (4-*p*-HYDROXYPHENYL-2,2,4-TRIMETHYLCHROMAN)/ XENON

Dianin's compound (25 g) was dissolved in 1-decanol (35 g) at 125°C. The hot solution was placed in a high-pressure autoclave. The solution was pressurized with compressed xenon to 300 bars. (*See original document submitted for rest of the translation.*)